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A Therapeutic Opportunity in Melanoma: ErbB4 Makes a Mark on Skin

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Malignant melanomas are aggressive tumors that are largely refractory to conventional drug therapies. A recent study reported in *Nature Genetics* identified mutationally activated *ErbB4* alleles in 20% of cases. These tumor cells exhibit ErbB4 dependency, suggesting that ErbB4 kinase inhibition may constitute an effective therapeutic strategy in this setting.

Malignant melanomas are aggressive and treatment-refractory cancers, associated with a 5 year survival rate below 20% (Chin et al., 2006). In other similarly challenging diseases, inhibitors of mutationally activated kinases on which tumor cells exhibit dependency have demonstrated impressive clinical activity in some patients. Such findings have prompted intensive efforts to resequence the cancer "kinome" in various tumor types to identify additional settings where kinase inhibition might yield clinical benefit (Stratton et al., 2009). One of the most notable successes of such efforts was the discovery of recurrent activating alleles affecting the BRAF serine/threonine kinase in 7% of all tumors examined, including ~65% of melanomas (Davies et al., 2002). Consequently, BRAF kinase inhibitors are undergoing clinical evaluation, and preliminary findings suggest that BRAF inhibition can yield good clinical responses in the majority of melanoma patients harboring the recurrent BRAF V600E allele (K. Flaherty, personal communication). While these early findings appear promising, alternative therapeutic strategies for malignant melanoma will undoubtedly be needed.

In a recent issue of *Nature Genetics*, Prickett and colleagues reported finding somatic activating mutations of the ErbB4 receptor tyrosine kinase in 19% of malignant melanomas, revealing another possible "Achilles' heel" within these tumors (Prickett et al., 2009). Sequencing the kinase domain-encoding exons of all 86 predicted tyrosine kinases in 79 melanomas revealed 19 genes in which mutations were present, the vast majority of which had not been previously implicated in melanoma. The ratio of nonsynonymous to synonymous mutations suggested that most mutations corresponded to oncogenic "drivers" as opposed to coincidental "passengers."

Follow-up analysis was focused on mutations in *ErbB4*, which were detected in 15 of 79 melanoma samples (19%). ErbB4 is one of four closely related members of a family of growth factor receptors that includes EGFR/ErbB1, HER2/ErbB2/Neu, and HER3/ErbB3. Following ligand-dependent receptor homo- or heterodimerization, these receptors transduce kinase-mediated signals that modulate cell proliferation, survival, and migration—processes that can directly impact the malignant properties of cancer cells. Indeed, each of the ErbB family receptors has been implicated in human tumorigenesis. Thus, mutational activation of EGFR is causally associated with many gliomas and non-small cell lung cancers, and at lower frequency in additional tumor types. Activated HER2/ErbB2 directly contributes to ~20% of breast cancers and possibly some ovarian cancers and other solid tumors. Both receptors can transduce critical cell survival signals, via heterodimerization with ErbB3, and engagement of PI-3 kinase/AKT signaling. Notably, a role for ErbB4 in cancer has, until now, been less certain. In fact, several studies have concluded that ErbB4 may function as a tumor suppressor in breast and prostate cancer (Sundvall et al., 2008; Williams et al., 2003), possibly by antagonizing ErbB2 signaling. However, this remains controversial, as ErbB4 knockout mice do not experience mammary tumorigenesis, and ErbB4 disruption does not detectably enhance the development of ErbB2-driven mouse mammary tumors (Jackson-Fisher et al., 2006).

The findings by Prickett et al. are not the first to report mutations of *ErbB4* in human cancer. Thus, an analysis of 595 tumors from stomach, lung, colon, and breast revealed 12 cases with *ErbB4* mutations (nine within coding sequences) (Soung et al., 2006). Similarly, an analysis of 188 lung adenocarcinomas revealed 9 cases with *ErbB4* mutations; however, these were not functionally validated (Ding et al., 2008). Prickett and colleagues examined the functional relevance of the melanoma mutations, which were widely scattered throughout the coding regions of ErbB4, including the kinase and extracellular ligand-binding domains. Moreover, only one of the 20 coding sequence mutations detected (all missense mutations) was observed more than once (it was seen twice), in striking contrast to the highly recurrent nature of activating *BRAF* and *EGFR* mutations.

To validate their findings, these investigators undertook functional studies of seven of the *ErbB4* melanoma mutants to determine if they constitute activated oncogenic alleles. In transfected cultured cells, each of the mutant proteins exhibited increased autophosphorylating activity and increased transforming activity, as assessed in focus-forming and anchorage-independent growth assays, relative to wild-type ErbB4. Moreover, they promoted elevated phospho-AKT. Using RNA interference, they demonstrated that ErbB4 ablation in cells expressing mutant alleles, but not in cells expressing wild-type ErbB4, inhibited proliferation, and concluded that melanoma

cells expressing these *ErbB4* alleles exhibit ErbB4 dependency, potentially yielding a therapeutic opportunity.

To model the potential benefit of pharmacologic ErbB4 inhibition, they treated melanoma cell lines with lapatinib, a pan-ErbB kinase inhibitor. Lapatinib is approved for clinical use in trastuzumab (Herceptin)-refractory breast cancers, and demonstrates potent EGFR and ErbB2 kinase inhibition. Although its activity as an ErbB4 inhibitor is less well characterized, Prickett et al. found that *ErbB4* mutant melanoma cell lines were substantially more lapatinib-sensitive than melanoma cells expressing wild-type *ErbB4*. Notably, among a panel of melanoma cells expressing various *ErbB4* mutants, a wide range of drug sensitivity was observed, suggesting either that the distinct ErbB4 mutants display varying lapatinib sensitivities or that additional differences between these cell lines contribute to their drug response. Moreover, the investigators have not excluded a potential contributing role for inhibition of EGFR and/or ErbB2—both of which have been implicated in the malignant properties of melanoma cells—in lapatinib sensitivity. The development of ErbB4-specific kinase inhibitors will be required to definitively address this issue.

The clinical implications of these findings are potentially substantial. Lapatinib is a clinically approved drug and could be readily repurposed for use in *ErbB4* mutant melanoma. Additional ErbB family kinase inhibitors are currently undergoing development, and some of these are also likely to display ErbB4 inhibitory activity. However, in light of the abovementioned putative tumor suppressor function of ErbB4, systemic inhibition of this kinase could be problematic, as it might actually promote tumorigenesis in some tissues.

A curiosity that arises from these findings is that activating *ErbB4* and *BRAF* mutations can be found in the same tumor cells in some melanomas. Both kinases can confer a state of "oncogene addiction," suggesting either that some melanoma cells can exhibit strict dependency on two distinct signaling pathways or that ErbB4 and BRAF participate in cross-talk that effectively yields a single oncogenic pathway with multiple vulnerabilities.

The scattered nature of the identified *ErbB4* mutations throughout the coding sequence is also curious, and further studies will be needed to determine whether all of these mutations lead to kinase activation and/or increased signaling and how these various mutations, which affect distinct functional domains of ErbB4, contribute to a similar degree of elevated kinase and transforming function. Interestingly, in one-third of the melanomas found to harbor *ErbB4* mutations, more than one *ErbB4* coding sequence mutation was present within the same sample, raising the possibility that these mutations cooperate to enhance ErbB4's oncogenicity. The role of these various mutations is further confounded by a report demonstrating that some of the previously detected *ErbB4* mutations in other tumor settings confer loss of kinase activity while preserving ErbB4's ability to transduce downstream signals via ErbB2, but with a qualitatively distinct output (Tvorogov et al., 2009).

Overall, these are provocative new findings that reveal a potentially important therapeutic opportunity for a challenging disease. While clinical validation of these observations will certainly be required, this study opens up an exciting new avenue of investigation in melanoma research and highlights the increasingly complex role of the ErbB family receptors in cancer.

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